Original Article

Evaluation of the Efficacy of Zinc Sulfate in the Prevention of Chemotherapy-induced Mucositis: A Double-blind Randomized Clinical Trial

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Abstract

Background: Oral mucositis is a serious complication of chemotherapy that results in painful debilitating inflammation, necessitating the administration of analgesics. There is no cure for mucositis. Some studies have evaluated the effect of zinc sulfate on mucositis. The present study aims to evaluate the effect of oral zinc sulfate on prevention of mucositis, xerostomia, and pain induced by chemotherapy.

Methods: This double-blind, randomized controlled trial was carried out on 50 adult patients who underwent chemotherapy during 2008-2009. Patients were divided in two groups. Patients in the intervention group were administered three, 220 mg zinc sulfate capsules daily until the end of their chemotherapy treatment. Patients in the placebo group received three placebo capsules daily, which were similar in shape, taste, and color to the zinc sulfate capsules.

Data were analyzed by SPSS version 17 software, using the independent samples t-test, Mann-Whitney U and Friedman tests.

Results: The incidence of grade 3 mucositis was lower in the zinc sulfate group. In the first follow up, grade 3 mucositis was detected in 10% of patients. In the placebo group, grade 3 mucositis was seen in 46.6% of patients. By the fourth follow up, grade 3 mucositis was detected in 3.33% of patients in the intervention group and in 20% of patient in the placebo group. At the end of the study there was no grade 3 mucositis detected in the zinc sulfate group, whereas there were 3.57% of patients in the placebo group with grade 3 mucositis. The results also showed that zinc sulfate decreased the effects of xerostomia and pain in patients under chemotherapy treatment.

Conclusion: It can be concluded that zinc sulfate might decrease the intensity of mucositis.

Keywords: Chemotherapy, oral mucositis, zinc sulfate

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Introduction

Oral mucositis is one of the serious complications in those patients undergoing radiotherapy or chemotherapy. Research shows that 40% of cancer patients who are treated with chemotherapy and bone marrow transplantation suffer from oral mucositis.[1]

Oral mucositis is thought to be due to a complicated biologic process involving direct damage to the oral epithelium during cell division, depletion in the basal cells of the epithelium, weakness in the modulation of the immune system, increase in the inflammatory process, and superinfection presented by oral bacterial flora.[2] Oral mucositis results in painful debilitating inflammation, necessitating the administration of opioid analgesics.[3] Due to the inability of patients to enjoy oral nutrition, they resort to intestinal or venous nutrition. Severe mucositis can affect the patients' therapeutic schedule and in some cases may stop treatment.[4] Mucositis may cause vomiting, diarrhea, sleep disturbances, anorexia,[5] weight loss, and a decrease in quality of life.[6]

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Mucositis induced by chemotherapy in the non-keratinized mucosa usually begins in the first and second week of chemotherapy treatment, and subsides during the third or fourth week following chemotherapy. Pain resulting from mucositis leads to disorders in swallowing and normal functions of the oral cavity. These disorders along with xerostomia increase the risk of opportunistic infections.[7] Mucositis is often controlled by the use of chlorhexidine,[8] sodium carbonate,[9] saline mouthwashes,[10] and local anesthetics such as diphenhydramine,[11] promethazine mixed with manganese milk, in addition to covering agents such as sucralfate,[12] and anti-inflammatory agents such as matricaria recutita (chamomile),[13] or local steroids[14] and adequate water intake. However, none can cure mucositis completely.[4]

Several studies have evaluated the effect of zinc on wound healing and epithelial tissue health. These studies have shown that zinc sulfate supplementation causes rapid recovery of leg and gastric ulcers. In these studies it is noted that zinc sulfate supplementation has a greater effect on patients who have sufficient levels of zinc in their serum.[15]

It seems zinc not only increases re-epithelialization, it also decreases inflammation and bacterial activity by inducing rapid wound healing.[16] Zinc also monitors the immune system and T lymphocytes. Decreases in zinc serum levels lead to lymphopenia and declines in cellular and humoral immunity.[17] The effect of oral zinc sulfate has also been considered for treatment of oral injuries; moreover, research has shown zinc supplementation assists with the recovery of mucosal wounds and treatment of geographic

Table 1. Objective grades of xerostomia according to the LENT SOMA scale

Description	Grade
Normal moisture	1
Scant saliva	2
Absence of moisture, sticky, viscous saliva	3
Absence of moisture, coated mucosa	4

Table 2. Demographic characteristics of patients

Variable	Zinc sulfate group	Placebo group
Gender (n)		
Male	13	13
Female	12	12
Age (y)		
Range	18–70	18–79
Mean±SD	51.53.3±	47.23.5±
Tumor site (n)		
Lung	5 (20%)	4 (16%)
Nasopharynx	2 (8%)	1 (4%)
Hematologic cells	7 (28%)	9 (36%)
Esophagus	1 (4%)	3 (12%)
Stomach	2 (8%)	1 (4%)
Prostate	2 (8%)	3 (12%)
Breast	6 (24%)	4 (16%)

tongue.[18]

Some studies have evaluated the effect of zinc sulfate on mucositis arising from radiotherapy and chemotherapy.[2,19] Since these studies have not evaluated the effect of drugs on xerostomia, pain and patient quality of life, and it seems these studies do not sufficiently explain the effects of oral zinc sulfate. Therefore, the present study intends to evaluate the effects of oral zinc sulfate on prevention of mucositis induced by chemotherapy, considering the role of zinc in re-epithelization, increased and decreased inflammation, as well as its effect on bacterial activity.

Materials and Methods

This double-blind randomized controlled study was carried out on 50 adult patients, (over 18 years of age), who underwent chemotherapy treatment for the first time during 2008 – 2009. Inclusion criteria were: i) chemotherapy treatment by a regimen with the same mucositis probability, including cyclophosphamide, doxorubicin, dacarbazine, gemcitabine, methotrexate, and 5-fluorouracil; Karnofsky performance status 60 or above; iii) life expectancy equal to or more than 6 months; iv) white blood cell (WBC) count equal to or more than 1500cell/ml) platelet counts equal to or greater than 100,000/μL.

Exclusion criteria included: i) previous or simultaneous radiotherapy in the head and neck region, including the nasopharynx, oropharynx, and larynx; ii) previous head and neck surgery due to malignancy; iii) use of dentures; iv) pregnancy; and v) infection.

Subjects were selected from patients who referred to the Oncology Department at Zahedan Imam Ali Hospital, Zahedan, Iran.

The Ethics Committee of Zahedan University of Medical Sciences approved the study protocol prior to patient enrolment. All patients signed informed consent forms. This study has been registered in the Iranian Registry of Clinical Trials, registry number: IRCT201101023133N3 and is available online at: http://www.irct.ir/ and www.who.int/trialsearch/trial.

Patients were divided by block randomization into 2 groups of zinc sulfate and placebo. Each group consisted of 25 patients; all were followed until the end of chemotherapy treatment. Patients were informed about oral hygiene, including drinking water and brushing teeth with a soft toothbrush after each meal; as well as abstinence from alcohol, smoking cigarettes, hot or cold drinks, and very spicy, acidic, and tough foods during chemotherapy. Patients in the intervention group took three; 220 mg zinc sulfate capsules daily (Alhavi Co., Tehran, Iran) until the end of chemotherapy treatment. The placebo group took three placebo capsules that were provided by the zinc sulfate manufacturing company (Alhavi Co., Tehran, Iran) , and were similar in shape, taste, and color to the zinc sulfate capsules. Randomized divisions and zinc sulfate drug prescription of patients were carried out by patients' own oncologists.

Patient's mucous and salivary health was checked by an oral medicine specialist prior to the initiation of chemotherapy. Two weeks after initiation of chemotherapy and every two weeks until the end of chemotherapy, a dental student and an oral medicine specialist monitored patients for the appearance of oral mucositis, xerostomia, and pain. The student and specialist were blinded to the randomization and treatment. Patients were examined with an overhead light, by using dental explorers and mirrors.

Oral mucositis was graded from 0 to 4, using World Health Organization (WHO) criteria[20] and xerostomia was diagnosed from 1 to 4, as seen in Table 1.[21]

The degree of pain was evaluated based on a visual analog scale, where zero indicates no pain and ten is the most severe pain that can be endured. Patients showed the degrees of their pain by a ruler .Patients were requested to choose a number from 1 to 10 that expressed their pain intensity. For quality of life, patients individually met with the dental student at each follow up, where the student completed a questionnaire (EORTC LQ-OES18).[22]

Data were analyzed by SPSS version 17 software. The independent samples t-test was used to evaluate xerostomia and mucositis recovery time. Mann-Whitney U test evaluated xerostomia, mucositis, and pain intensity. The Friedman test evaluated the effect of time. *P* was considered significant at the 0.005 level for the Mann-Whitney U test. To prevent a repeated measurement error, we divided α into 10, and 0.05 for the Friedman and independent t-tests.

Table 3. Mucositis grades in both groups of patients.

Mucositis groups	Week2	Week4	Week6	Week8	Week10	Week12	Week14	Week16	Week18	Week20	*P*-value for Friedman test
Intervention											
95%CI	2.03–2.36	1.77–2.14	1.48–2.03	1.29–1.79	1.17–1.68	1.06–1.45	0.97–1.35	0.95–1.27	0.87–1.32	0.57–1.17	*P*<0.001
Mean	2.20	1.96	1.76	1.54	1.43	1.26	1.16	1.11	1.10	1.16	
Placebo											
95%CI	2.05–2.50	2.23–2.64	2.12–2.51	1.99–2.40	1.75–2.08	1.75–2.08	1.75–2.08	1.54–2.27	1.04–2.62	0.89–3.76	*P*=0.35
Mean	2.28	2.44	2.32	2.20	1.92	1.92	1.92	1.90	1.83	2.33	
***P*-value for Mann-Whitney test**	0.494	0.02	0.02	0.001	0.01	0.001	0.016	0.001	0.020	0.004	----

Table 4. Xerostomia, pain intensity, and quality of life in both groups of patients

	Intervention		Placebo		*P*-value(Mann-Whitney test)
	Mean	95%CI	Mean	95%CI	
Xerostomia					
Week 0	1.2	1.03–1.36	1.4	1.93–1.60	0.127
Week 2	3.24	3.02–3.45	3.6	3.39–3.80	0.019
Week 4	2.44	2.19–2.68	3.32	3.09–3.54	<0.001
Week 6	2.4	2.19–2.60	3.12	2.90–3.33	<0.001
Week 8	2.16	1.92–2.40	3.08	2.81–3.34	<0.001
Week 10	.04	1.83–2.24	3	2.83–3.16	<0.001
Week 12	1.91	1.78–2.03	2.58	2.33–2.82	<0.001
Week 14	1.83	1.64–2.02	2.75	2.15–3.34	<0.001
Week 16	1.72	1.49–1.95	2.5	2.05–2.94	0.002
Week 18	1.52	1.26–1.76	2.5	2.05–2.94	0.115
Week 20	1.16	0.73–1.59	2.5	2.05–2.94	0.0049
Pain					
Week 2	6.72	6.21–6.22	7.00	6.40–7.59	0.43
Week 4	6.16	5.61–6.07	7.64	7.21–8.06	0.01
Week 6	5.56	5.097–6.02	7.48	7.04–7.91	0.003
Week 8	5.25	4.85–5.64	6.32	6.84–7.79	<0.001
Week 10	5.00	4.56–5.43	6.50	6.73–7.66	<0.001
Week 12	4.78	4.35–5.21	6.91	6.46–7.36	<0.001
Week 14	4.76	4.23–5.29	7.42	6.40–7.59	<0.001
Week 16	4.52	4.07–4.97	7.42	6.70–8.15	0.020
Week 18	4.16	3.37–4.95	7.00	6.40–7.59	0.447
Week 20	4.00	3.12–4.87	7.00	6.40–7.59	0.0049
Quality of life					
Week 2	40	37–43.3	39.6	36.5–42.7	0.79
Week 4	46.6	43.4–49.8	46.6	43–50.8	0.91
Week 6	43.1	41.1–46.1	45.6	41.8–49.4	0.29
Week 8	40.1	37.5–42.8	43.4	39.6–47.1	0.75
Week 10	38	35.5–40.4	42.3	38.6–46.1	0.16
Week 12	36.2	33.3–38.9	41	37.3–45.01	0.32
Week 14	34.3	31.9-36.4	41.2	30.3–52.3	0.36
Week 16	34.1	30.6–37.7	46.6	24.9–53.6	0.15
Week 18	34.1	30.6–37.7	46.6	24.9–53.6	0.15
Week 20	33	32–34.3	34.2	36.7–42.3	0.88

Results

Distribution of age, gender, and disease type were the same in both groups (Table 2). The analytical results of this study for mucositis, xerostomia, time and life quality effects, degree of pain, and treatment period are presented below.

Mucositis intensity

At the beginning of the study none of the patients had symptoms of mucositis. In the first, second, and third visits, there were no statistically significant differences in mucositis intensity between groups; however, in the 8th, 12th, 16th, and 20th weeks of chemotherapy there were statistically significant differences between both groups ($P < 0.005$; Table 3).

Xerostomia intensity

One week before the study, we examined patients for xerostomia. Patients' salivary flows were in the normal range, with no statistically significant differences between groups ($P = 0.13$). At the first visit which was held during the second week of chemotherapy, there were no statistically significant differences in xerostomia intensity between the drug and placebo groups ($P = 0.019$). In the second visit (chemotherapy week 4), there were statistically significant differences noted between both groups ($P < 0.005$). The intensity of xerostomia in the drug group was less than the placebo

group ($P < 0.005$), a trend which continued until the eighth session in the sixteenth week of treatment.

In the ninth visit (chemotherapy week 18) xerostomia intensity was not statistically significant between both groups ($P = 0.115$). However, in the tenth meeting (chemotherapy week 20), the intensity of xerostomia was significantly lower in the drug group compared with the placebo group ($P < 0.005$; Table 4).

Pain intensity

Patient pain intensity from the third visit (chemotherapy week 6) until the tenth meeting (chemotherapy week 20) exhibited statistically significant differences between the drug and placebo groups, which indicated that pain intensity in the drug group was less than in the placebo group ($P < 0.005$; Table 4).

Recovery period

Mucositis

The mucositis recovery period is the time interval between appearance of mucositis signs and symptoms and their complete resolution. The recovery period was seven weeks and three days for the zinc treatment group and eight weeks for the placebo group. There was no statistically significant difference in the mucositis treatment period between both groups ($P = 0.13$).

Xerostomia

The recovery period for xerostomia is the time interval between the appearance of xerostomia signs and symptoms and their complete resolution in both groups. Between treatment and placebo groups, there were no significant differences noted in terms of xerostomia treatment ($P = 0.23$; 7 weeks in the placebo group versus 6 weeks and 5 days in the zinc group).

Time effect

We used the Friedman test to determine the effect of time on mucositis, xerostomia, and pain intensity. The results showed increased drug effect with decreased mucositis and xerostomia intensity, and degree of pain over increased time in the zinc sulfate group ($P < 0.005$).

Quality of life

We evaluated quality of life with the EORTC QLQ-OES18 questionnaire. Validity and reliability of this questionnaire was approved by Pakpour et al. among Iranian patients.[22] Quality of life was not statistically different between zinc and placebo groups (Table 4).

Discussion

The present study was undertaken to determine if zinc sulfate was able to decrease the effect of oral mucositis in cancer patients under chemotherapy.

The results of the present study showed that although the use of zinc sulfate did not decrease the incidence of mucositis in patients, it improved the intensity of oral mucositis and xerostomia. Since the intensity of mucositis in the placebo group was greater than seen in the zinc group it can be concluded that zinc sulfate might decrease mucositis intensity.

Research has shown that almost 100% of patients who undergo radiotherapy and chemotherapy due to bone marrow transplantation will be afflicted with oral mucositis.[1]

At present, the effectiveness and safety of diets available for the prevention or treatment of oral

mucositis have not been substantiated. Current preventive methods are chlorhexidine,

sodium carbonate, saline mouthwashes, and ice.[8]

There are a few reports on the use of zinc sulfate for oropharyngeal mucositis. Ertekin et al. in 2004 used zinc sulfate for the prevention of mucositis and dermatitis that resulted from radiotherapy (radiation-induced oropharyngeal mucositis and dermatitis). They examined zinc sulfate on 30 patients under radiotherapy and found no grades 3 and 4 mucositis (severe) in the drug group, however grades 3 and 4 mucositis were observed in some patients in the placebo group. According to these researchers, mucositis intensity in the drug group was less than in the placebo group.[19]

Another study on mucositis and dermatitis was carried out by Lin et al. in 2006 which utilized zinc supplementation (pro-z) in patients after radiotherapy. Late-onset, less severe mucositis and dermatitis were seen in patients who received zinc, but there was no statistically significant difference between the groups.[2]

Our results agreed with these findings. Although the use of zinc sulfate did not decrease the incidence of mucositis, however mucositis intensity in the drug group was less than in the placebo group.

These studies did not evaluate the effect of zinc on xerostomia and pain. Our findings showed that zinc sulfate administered three times daily significantly decreased both xerostomia and pain intensity. Despite differences in mucositis intensity between the two groups at the ninth visit, the degree of pain and xerostomia were the same in both groups. It can be concluded that pain may be related to saliva, mucosal humidity, and the existence of anti-inflammatory factors rather than mucositis intensity.

In the present study the effect of time was evaluated. It was shown that the drug effect increased over time. Patients who received zinc for mucositis, xerostomia, and pain had decreased symptoms with increased time.

It has been reported that mucositis may cause vomiting, diarrhea, pain, sleep disturbances, anorexia, weight loss, and decreased quality of life.[4] The present study attempted to determine the effect of zinc on quality of life. According to our results, despite the statistically significantly difference in mucositis intensity between the groups, the quality of life was the same. In addition to oral and nutritional difficulties, there were several factors which affected quality of life. Furthermore, severe oral mucositis (grades 3 and 4) has been shown to influence patient quality of life from a functional and chief complaint point of view.

Due to the low incidence rate of oral mucositis cases in the present study, the absence of statistically significant differences between these groups is justifiable.

The results of the present study show that using zinc sulfate can significantly decrease mucositis intensity and xerostomia in patients who suffer from different malignancies and are under chemotherapy treatment. Further research is required to validate our findings.

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